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BEFORE THE BOARD OF PATENT APPEALS

AND INTERFERENCES

Paper No. 31

Serial Number: 09/300,978

Filing Date: 4/28/99

Appellant(s): Spitler and Maida

Laurie L. Hill

For Appellant

EXAMINER'S ANSWER

This is in response to appellant's Brief on Appeal filed 7/2/03 (Paper No. 30).

The text of those sections of Title 35 U.S. Code not included in this appeal can be found in a previous Office Action herein.

(1) Real Party of Interest.

A statement identifying the real party of interest in contained in the Brief.

(2) Related Appeals and Interferences Identified.

A statement identifying that no related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the Brief.

(3) Status of Claims.

The statement of the status of claims contained in the Brief is correct.

Claims 13, 15, 16 and 18-24 as they read on PSMA as the elected invention are pending and are on appeal.

(4) Status of Amendments After Final.

The appellant's statement of the status of amendments after final rejection contained in the Brief is correct.

(5) Summary of Invention.

The summary of invention contained in the Brief is correct.

(6) Issues.

The appellant's statement of the issues in the Brief is correct with respect to Issue 2.

Upon reconsideration, the previous rejection under 35 U.S.C. § 112, first paragraph, with respect to claimed "nucleic acid sequences" as they read on the known PAP and PSMA prostate antigens of the claimed in the claimed methods, has been withdrawn.

(7) Grouping of Claims.

In agreement with the Brief, the rejection of claims 13, 15, 16 and 18-24 stand or fall together with respect to the rejection under 35 U.S.C.§ 103.

(8) Claims Appealed.

The copy of the appealed claims contained in the Appendix to the Brief is correct.

(9) Prior Art of Record.

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

A) Andriole et al. (Ann. Rev. Med. 42: 9-15, 1991).

B) Fundamental Immunology, Second Edition (Paul, Ed, Raven Press, New York, 1989) (page 931, column 1, paragraph 1; Differentiation Antigens and Other Tumor-Associated Antigens).

C) Grauer et al. (U.S. Patent No. 5,250,297).

D) Horoszewicz (U.S. Patent No. 5,162,504).

E) Illustrated Dictionary of Immunology (Cruse et al., CRC Press Boca Raton 1995) (page 302).

F) Immunology, Second Edition (Kuby, W.H. Freeman and Company, New York, 1991) (see page 590, column 2 and page 613, column 2; Tumor-Associated Antigens and Tumor-Specific Antigens).

G) Israeli et al. (U.S. Patent No. 5,538,866).

H) Linnenbach et al. (U.S. Patent No. 5,668,002).

I) Linnenbach (U.S. Patent No. 5,185,254).

J) McCarley et al. (Seminars in Surgical Oncology 5:293-301, 1989).

K) Sela et al. (Hybridoma 8: 481-491, 1989).

L) Spitler (U.S. Patent No. 5,738,867).

M) Varki et al. (Cancer Research 44: 681-687, 1984).

(10) Grounds of Rejection.

The following ground(s) of rejection are applicable to the appealed claims.

Rejection Under 35 U.S.C. § 103

Claims 13, 15, 16 and 18-24 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Spitler (U.S. Patent No. 5,738,867) in view of Israeli et al. (U.S. Patent No. 5,538,866), Horoszewicz (U.S. Patent No. 5,162,504), Andriole et al. (Ann. Rev. Med. 42: 9-15, 1991) and in view of art acknowledged methods of delivering antigens of interest to stimulate antitumor responses, as disclosed on pages 10-19 of the instant specification and in further evidence of McCarley et al. (Seminars in Surgical Oncology 5:293-301, 1989)

alone or in combination with

Illustrated Dictionary of Immunology (Cruse et al., CRC Press Boca Raton 1995) (page 302),

Immunology, Second Edition (Kuby, W.H. Freeman and Company, New York, 1991) (see page 590, column 2 and page 613, column 2; Tumor-Associated Antigens and Tumor-Specific Antigens)

Fundamental Immunology, Second Edition (Paul, Ed, Raven Press, New York, 1989) (page 931, column 1, paragraph 1; Differentiation Antigens and Other Tumor-Associated Antigens),

Grauer et al. (U.S. Patent No. 5,250,297),

Varki et al. (Cancer Research 44: 681-687, 1984),

Linnenbach (U.S. Patent No. 5,185,254),

Linnenbach et al. (U.S. Patent No. 5,668,002), and

Sela et al. (Hybridoma 8: 481-491, 1989)

essentially for the reasons set forth in the previous Office Actions (Paper Nos. 7/11/13/22/23/27).

Additional references have been cited to counter appellant's assertions that the primary reference Spitler's (U.S. Patent No. 5,738,867) teaching of tumor associated antigens read on cancer unique antigens and do not read on prostate antigens such as PSMA. Again, Spitler does not use the term "unique" as asserted by appellant. Spitler does not use the term "tumor specific antigen". Spitler teaches "tumor associated antigens" and given the standard well known understanding of "tumor associated antigens", PSMA reads on Spitler's teaching of eliciting antitumor responses to prostate tumor associated antigens. Further, in contrast to appellant's assertions, the antigens cited by Spitler are not unique to tumor tissue but fall into the well known understanding and scope of tumor associated antigens,.

Spitler teaches methods of delivering antitumor vaccines with tumor associated antigens, including prostate antigens (see Summary of the Invention), as well as known methods of delivering said tumor associated antigens to stimulate antitumor responses, encompassed by the claimed invention (see entire document). Spitler teaches that patients with cancer may have the cancer surgically excised and the be given the subject tumor vaccines (see column 10, lines 39-47).

Spitler differs from the instant claimed methods by not disclosing a particular prostate antigen, nor the elected species PSMA per se.

Israeli et al. teach PSMA , including nucleic acids and methods of expressing said PSMA, as well as its expression on prostate tumors (see entire document, including Background of the Invention and Detailed Description of the Invention). Israeli et al. teach that the main metastatic site for prostatic tumor is the bone (column 23, paragraph 2).

Horoszewicz (U.S. Patent No. 5,162,504) teaches that there is a need for monoclonal antibodies which are prostate specific and which do not cross react with other tissue types (see column 6, paragraph 2 and provides for the monoclonal antibodies specific for prostatic tumor antigens and distinguishable from prior prostate antigens (see entire document, including Summary of the Invention and Claims). Horoszewicz further discloses that prostatic epithelium has limited distribution, does not carry out functions vital for the survival of a patient and has been shown to produce organ specific molecules (see column 3, paragraph 3). In addition, the evidence for the selective specificity for the 7E11-C5 for human prostatic epithelium was reinforced by consistently negative results of immunospecific staining of numerous fresh frozen sections from a wide range of human non-prostatic normal or malignant tissues (see column 24, paragraph 3 and Results).

Andriole et al. review the diagnosis and treatment of prostate cancer and teach that surgical excision of the prostate is unsurpassed as a means of controlling organ-confined prostate cancer (see page 13, paragraph 2).

McCarley et al. teach that in prostate cancer, monoclonal antibodies prostate antigens are not usually tumor specific (See Abstract and page 298, column 2, paragraph 3 - page 299).

Pages 10-19 of the specification discloses the art known methods of delivering antigens, including tumor associated antigens, of interest to stimulate antitumor responses encompassed by the claimed methods.

Given the teachings of Israeli et al. and Horoszewicz that the PSMA / 7E11 specificity is a marker or antigen for prostate cancer; one of ordinary skill in the art at the time the invention was made would have been motivated to substitute the prostate tumor associated antigen PSMA into the methods of stimulating antitumor responses, as known and practiced in the prior art, as taught by Spitler and acknowledged by the specification as to treat prostate cancer.

Given the tissue and tumor specificity of the PSMA / 7E11 specificity as well as immunogenicity as well as its advantages over previous prostate antigens as taught by Israeli and Horoszewicz coupled with McCarley et al. teaching that in prostate cancer, monoclonal antibodies prostate antigens are not usually tumor specific (See Abstract and page 298, column 2, paragraph 3 - page 299); one of ordinary skill in the art at the time the invention was made would have been motivated to apply the PSMA prostate antigen in the methods of Spitler to elicit antitumor responses to prostate antigens (Summary of the Invention).

It would have been obvious to the ordinary artisan to use PSMA in patients with metastatic prostate tumors and/or patients who have had the prostate tumor removed surgically to elicit antitumor responses in order to treat said cancer patients. Again, Spitler teaches that patients with cancer may have the cancer surgically excised and the be given the subject tumor vaccines (see column 10, lines 39-47) and Andriole et al. teach that surgical excision of the prostate is unsurpassed as a means of controlling organ-confined prostate cancer (see page 13, paragraph 2). Also, it would have been obvious to the ordinary artisan to select portions, particularly extracellular portions of PSMA to stimulate antitumor responses, given that these extracellular portions are exposed to immune responses.

From the teachings of the references and known in the prior art; it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Additional references have been cited to counter appellant's assertions that Spitler's teaching of tumor associated antigens read on cancer unique antigens and do not read on prostate antigens such as PSMA.

Again, Spitler does not use the term "unique" as asserted by appellant. Spitler does not use the term "tumor specific antigen". Spitler teaches "tumor associated antigens" and given the standard well known understanding of "tumor associated antigens", PSMA reads on Spitler's teaching of eliciting antitumor responses to prostate tumor associated antigens. Further, the antigens cited by Spitler are not unique to tumor tissue but fall into the well known understanding of tumor associated antigens.

Additional references have been cited in the rejection under 35 USC 103 to further support the PSMA antigen as an antigen specific for prostate tissue, including prostate cancer and that vaccination for prostate antigens such as PSMA would have been combined with standard excision of the prostate tumor at the time the invention was made.

Given appellant's arguments concerning the primary reference employed in the obviousness rejection of record, the examiner requested for a definition of tumor associated antigen in the context of their arguments.

In response, appellant provided for a definition of Tumor-associated antigen in Appendix B of Paper No. 20, filed 4/10/02, which reads as follows.

Tumor-associated antigen: A molecule specifically or preferentially expressed by tumoral cells, but not, hardly, by normal cells. Such molecules can be used as vaccination targets to destroy the tumor.

It is noted that appellant provided this definition obtained from the Aventis website, however the examiner could not locate this particular definition at the Aventis website. Appellant has not provided any further documentation to support this Aventis based definition of "tumor-associated antigen".

In turn, appellant has relied upon this definition to support previous assertions that the primary reference of Spitler (U.S. Patent No. 5,738,867) refers to the use of a tumor associated antigen to an antigen which is not found in normal tissue as the active ingredient in a vaccine.

Appellant argued that the present invention represents a different approach from the art by relying upon uniquely tumor-associated antigens as active ingredients, the present invention employs antigens namely PSMA and PAP that are associated with the host prostate tissues, that is, the antigens are found in normal prostate in contrast to other tissues. Generally, these antigens are found both in the normal prostate and in malignant prostate tissue (see page 4, lines 11-22 of the instant specification). The invention takes advantage of the fact that the prostate is not an essential organ and thus an immune response which could include disruption of normal tissue is acceptable (see page 4, lines 11-22 of the instant specification).

Again, appellant has mischaracterized the term tumor-associated antigen as understood by one of ordinary skill in the art at the time the invention was made and the primary Spitler reference. Further, the application of appellant's submitted definition of tumor associated antigens in the context of prostate antigens also mischaracterizes the term tumor-associated antigen as understood by one of ordinary skill in the art at the time the invention was made and the reference.

The Illustrated Dictionary of Immunology (Cruse et al., CRC Press Boca Raton 1995) (page 302) defined tumor associated antigens as follows:

Tumor-associated antigens: Certain antigens designated as CA-125, CA-19-9 and CA195, among others may be linked to certain tumors such as lymphomas, carcinomas, sarcomas, and melanomas, but the immune response to these tumor-associated antigens is not sufficient to mount a successful cellular or humoral immune response against the neoplasms. Three classes of tumor-associated antigens have been described. Class 1 antigens are very specific for a certain neoplasms and are absent from normal cells. Class 2 antigens are found on related neoplasms from separate individuals. Class 3 antigens are found on malignant as well as normal cells, but show increase expression in the neoplastic cells. Assays of clinical values will be developed for class 2 antigens, since they are associated with multiple neoplasms and very infrequently are found in normal individuals.

Immunology, Second Edition (Kuby, W.H. Freeman and Company, New York, 1991) (see page 590, column 2 and page 613, column 2; Tumor-Associated Antigens and Tumor-Specific Antigens) defined tumor associated antigens as follows:

Tumor-associated antigens: cell-surface proteins that are present on tumor cells and normal cells.

Tumor-specific antigens: cell-surface proteins found on tumor cells not on normal cells.

The majority of tumor antigens are not unique to tumor cells but also are present on normal cells and are called tumor-associated antigens. These antigens may be expressed only on fetal cells but not on adult cells, or they may be antigens expressed at low levels on normal cells but at much higher levels by tumor cells. (page 590, column 2).

Fundamental Immunology, Second Edition (Paul, Ed, Raven Press, New York, 1989) (page 931, column 1, paragraph 1; Differentiation Antigens and Other Tumor-Associated Antigens) discloses that some antigens expressed on tumor cells are also expressed on normal cells during at least some stage of differentiation markers. The extent to which these differentiation antigens are expressed by normal cells and tissued can vary from widespread expression to extreme restriction by a small clone of normal cells. Furthermore, the time during development when these markers are expressed on normal cells can vary considerably. Since none of these antigens is tumor specific, they are commonly referred to as "tumor-associated" antigens. These antigens represent a very diverse group of glycoproteins and glycolipids.

In discussing Diagnostic and Therapeutic Utility of Monoclonal Antibodies in Urologic Oncology, McCarley et al. (Seminars in Surgical Oncology 5:293-301, 1989) disclose that to date, monoclonal antibodies which are absolutely specific for cancer cells have not been found (page 293, column 2, paragraph 4).

Further, McCarley et al. disclose that in prostate cancer, monoclonal antibodies prostate antigens are not usually tumor specific (See Abstract and page 298, column 2, paragraph 3 - page 299).

Horoszewicz (U.S. Patent No. 5,162,504) teaches that there is a need for monoclonal antibodies which are prostate specific and which do not cross react with other tissue types (see column 6, paragraph 2 and provides for the monoclonal antibodies specific for prostatic tumor antigens and distinguishable from prior prostate antigens (see entire document, including Summary of the Invention and Claims). Horoszewicz further discloses that prostatic epithelium has limited distribution, does not carry out functions vital for the survival of a patient and has been shown to produce organ specific molecules (see column 3, paragraph 3). In addition, the evidence for the selective specificity for the 7E11-C5 for human prostatic epithelium was reinforced by consistently negative results of immunospecific staining of numerous fresh frozen sections from a wide range of human non-prostatic normal or malignant tissues (see column 24, paragraph 3 and Results).

In addition, appellant asserted that in sharp contrast to tumor associated antigens which are either not present or barely present in normal tissue, that it is clear from Spitler (U.S. Patent No. 5,738,867) cited in the obviousness rejection under 35 USC 103, that the tumor associated antigens contemplated therein were associated with tumors and not normal tissues, such as carcinoembryonic antigen and melanoma antigen, citing column 4, lines 7-10 of Spitler.

Here, in contrast to appellant's assertions, Spitler discloses the tumor associated antigens (TAAs) of CO 17-1A and KS1/4, both of which are expressed on both tumor and normal tissues.

In the Background of the Invention on column 1, lines 37-52), Grauer et al. (U.S. Patent No. 5,250,297) discloses that certain antigens are expressed by both human tumor cells and normal cells. These antigens are accordingly referred to not as "tumor specific" but as "tumor-associated" antigens. The diagnostic and therapeutic value of such tumor-associated antigens generally results from the excess quantity of antigen expressed by tumor cells relative to normal cells and the in vivo selectivity of antibodies for antigens for antigens expressed by tumor cells over normal cells.

Grauer et al. goes on to disclose that only a limited number of tumor associated antigens are well characterized, including the KS1/4 specificity (column 1, lines 53-67).

Varki et al. (Cancer Research 44: 681-687, 1984) disclose that the monoclonal antibodies KS1/4 is reasonably specific for lung cancer cells since it binds strongly to tumor tissues but either failed to react or reacted weakly with a variety of normal tissues (see entire document, including Abstract, Results and Discussion).

Further, Spitler (U.S. Patent No. 5,738,867) discloses several representative tumor associated antigens, including those of particular interest, including CO-029 and GA733-2 (see column 3, paragraph 3), both of which are expressed on normal tissues to some degree.

For example, Linnenbach (U.S. Patent No. 5,185,254) discloses that the tumor associated antigen GA733 is expressed on human stomach adenocarcinoma cells and that antibodies that bind GA733 bind to a variety of tumors and to varying degrees to normal epithelial tissues (e.g. see the first paragraph of the Background of the Invention).

Linnenbach et al. (U.S. Patent No. 5,668,002) discloses that the tumor associated antigen CO-029 was found to be expressed on gastric, colon, rectal and pancreatic carcinomas but not on most normal tissues (Sela et al., Hybridoma 8: 481-491, 1989) (e.g. see the first paragraph of the Background of the Invention).

Sela et al. (Hybridoma 8: 481-491, 1989) discloses that the antibody CO-029 binds gastrointestinal tract tumor cell lines and restricted binding specificities to human tissues and tumors (see entire document, including page 482, lines 3-5 and pages 483, overlapping paragraph, Binding Specificity of Mab CO-029).

Therefore, appellant's assertions that tumor associated antigens as taught by the primary reference Spitler is limited to antigens specific or unique to tumor cells (e.g. tumor-specific antigens) as opposed to associated with tumor cells (e.g. tumor associated antigens) have been clearly inconsistent with the art recognized understanding of tumor-associated antigens and have been clearly inconsistent with the Examples set forth in the primary Spitler (U.S. Patent No. 5,738,867) reference.

Spitler teaches methods of delivering antitumor vaccines with tumor associated antigens, including prostate antigens (see Summary of the Invention), as well as known methods of delivering said tumor associated antigens to stimulate antitumor responses, encompassed by the claimed invention (see entire document).

Again, with respect to prostate tumor associated antigens, the following is noted.

McCarley et al. disclose that in prostate cancer, monoclonal antibodies prostate antigens are not usually tumor specific (See Abstract and page 298, column 2, paragraph 3 - page 299).

Horoszewicz (U.S. Patent No. 5,162,504) teaches that there is a need for monoclonal antibodies which are prostate specific and which do not cross react with other tissue types (see column 6, paragraph 2 and provides for the monoclonal antibodies specific for prostatic tumor antigens and distinguishable from prior prostate antigens (see entire document, including Summary of the Invention and Claims). Horoszewicz further discloses that prostatic epithelium has limited distribution, does not carry out functions vital for the survival of a patient and has been shown to produce organ specific molecules (see column 3, paragraph 3). In addition, the evidence for the selective specificity for the 7E11-C5 for human prostatic epithelium was reinforced by consistently negative results of immunospecific staining of numerous fresh frozen sections from a wide range of human non-prostatic normal or malignant tissues (see column 24, paragraph 3 and Results).

Given the teaching of Spitler for employing tumor associated antigens associated with prostate, it would have been a reasonable understanding by the ordinary artisan at the time the invention was made to employ prostate antigens such as PSMA which was weakly expressed on normal prostate epithelium but strongly expressed on malignant prostatic epithelium. In turn, this differential normal versus malignant expression of PSMA fits within the definition and scope of tumor associated antigens as understood by one of ordinary skill in the art at the time the invention was made and was consistent with the primary reference of Spitler which teaches methods of delivering antitumor vaccines with tumor associated antigens, including prostate antigens (see Summary of the Invention), as well as known methods of delivering said tumor associated antigens to stimulate antitumor responses, encompassed by the claimed invention (see entire document). .

To reiterate, given the tissue and tumor specificity of the PSMA / 7E11 specificity as well as immunogenicity as well as its advantages over previous prostate antigens taught by Israeli and Horoszewicz coupled with McCarley et al. teaching that in prostate cancer, monoclonal antibodies prostate antigens are not usually tumor specific (See Abstract and page 298, column 2, paragraph 3 - page 299); one of ordinary skill in the art at the time the invention was made would have been motivated to apply the PSMA prostate antigen in the methods of Spitler to elicit antitumor responses to prostate antigens.

It would have been obvious to the ordinary artisan to use PSMA in patients with metastatic prostate tumors and/or patients who have had the prostate tumor removed surgically to elicit antitumor responses in order to treat said cancer patients. Again, Spitler teaches that patients with cancer may have the cancer surgically excised and the be given the subject tumor vaccines (see column 10, lines 39-47) and Andriole et al. teach that surgical excision of the prostate is unsurpassed as a means of controlling organ-confined prostate cancer (see page 13, paragraph 2). Also, the ordinary artisan would have been motivated to select portions, particularly extracellular portions of PSMA, that provided prostate specificity to stimulate antitumor responses in methods of treating prostate cancer at the time the invention was made.

(11) Response to Argument

Rejection Under 35 U.S.C. § 103

Appellant's arguments have been fully considered but are not found persuasive essentially for the reasons of record.

Given the prosecution history of the instant application as addressed above, appellant's arguments concerning the meaning of tumor associated antigens, including its application to prostate specific antigens at the time the invention was made have not been found persuasive for the reasons of record.

Previously, appellant has relied upon a definition to support previous assertions that the primary reference of Spitler (U.S. Patent No. 5,738,867) refers to the use of a tumor associated antigen to an antigen which is not found in normal tissue as the active ingredient in a vaccine.

Appellant argued that the present invention represents a different approach from the art by relying upon uniquely tumor-associated antigens as active ingredients, the present invention employs antigens namely PSMA and PAP that are associated with the host prostate tissues, that is, the antigens are found in normal prostate in contrast to other tissues. Generally, these antigens are found both in the normal prostate and in malignant prostate tissue (see page 4, lines 11-22 of the instant specification). Appellant has noted that the invention takes advantage of the fact that the prostate is not an essential organ and thus an immune response which could include disruption of normal tissue is acceptable (see page 4, lines 11-22 of the instant specification).

Again as pointed out above, it was noted that appellant has mischaracterized the term tumor-associated antigen as understood by one of ordinary skill in the art at the time the invention was made and the reference. Further, the application of appellant's submitted definition of tumor associated antigens in the context of prostate antigens also mischaracterized the term tumor-associated antigen as understood by one of ordinary skill in the art at the time the invention was made and the reference.

Subsequently, appellant modified their position from one wherein Spitler did not teach that tumor associated antigens read on cancer unique antigens and did not read on prostate antigens such as PSMA to a position where Spitler does not provide a teaching of organ-specific antigens, such as prostate antigens, or does not provide sufficient motivation for the use of PSMA.

Appellant now argues that the use of antigens that are organ-specific is a critical element of the claimed methods that cannot be ignored in the obviousness analysis. Appellant notes that the elicitation of an immune response to an organ-specific antigen results in the eradication of all antigen-expressing cells whether malignant or not. Because most organs are essential for continued viability, such a vaccination strategy is fatal for the recipient unless the targeted organ is non-essential, e.g. the prostate.

Appellant argues that the primary reference Spitler fails to teach or suggest the use of organ-specific antigens such as PSMA or PAP to elicit an antitumor response in a subject.

Again on page 10, paragraph 1 of the Brief, appellant argues that Spitler teaches the use of antigens that are uniquely associated with the malignant or metastatic nature of the cells, citing the disclosure of two antigens (i.e. CO-029 and GA733-2) that are characterized by expression on multiple malignancies (see column 2, lines 22-26 of Spitler). Appellant asserts that Spitler teaches the use of a pan-epitope to stimulate a general antitumor immune response against any malignant cell.

Again, appellant has mischaracterized the primary Spitler reference. In contrast to appellant's assertions, Spitler teaches methods of delivering antitumor vaccines with tumor associated antigens, including prostate antigens (see Summary of the Invention), as well as known methods of delivering said tumor associated antigens to stimulate antitumor responses, encompassed by the claimed invention (see entire document).

Appellant has asserted that Spitler teaches away from the claimed methods since Spitler teaches a need for a vaccine that is "efficacious in the prevention and treatment of all cancers" (column 1, lines 50-51 of Spitler) and Spitler teaches that the disclosed compositions are those useful "for the prevention and treatment of a variety of cancers" (column 2, lines 19-21 of Spitler).

It is not readily apparent that Spitler either teaches or is limited to a teaching of the use of a pan-epitope to stimulate a general antitumor immune response against any malignant cell. Rather, Spitler teach that the compositions are useful as vaccine-like compounds for the prevention and treatment of a variety of cancers (see Summary of the Invention on column 2). While it is understood that it would be much appreciated to have a single cancer vaccine to treat all cancers, it is very unlikely that the ordinary artisan at the time the invention was made would have read Spitler as being limited to such a panacea. Appellant appears to have a very narrow and unsupported reading of Spitler in asserting that Spitler is teaching a universal cancer antigen.

Here, it is a more reasonable to read a "variety of cancers" as referring to treating different species of cancer (e.g. prostate) within the genus of cancer.

Rather than focusing on tumor associated antigens as panaceas, Spitler is drawn methods and compositions employing liposomes compositions encapsulating or conjugated to tumor associated antigens (TAAs) (see entire document, including Summary of the Invention and Detailed Description of the Invention), including tumors associated with different organs systems, including the prostate (see entire document, including Summary of the Invention on column 2 and Example XII on columns 10-11).

In addition, if appellant's narrow reading of a universal vaccine by Spitler was true, then the ordinary artisan would need only one universal tumor associated antigen and not tumor associated antigens associated with a variety of tissues, as taught by Spitler.

A prior art reference may be considered to teach away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." See In re Gurley , 31 USPQ2d 1130, 1131 (Fed. Cir. 1994).

Here in contrast to appellant's assertions of teaching away by the prior art; there is no discouragement nor skepticism in the prior art for employing a variety of tumor associated antigens from a variety of different tissues to stimulate antitumor responses. Again, the primary Spitler reference is more directed to providing said tumor associated antigens encapsulated or conjugated to liposomes to achieve effective antitumor responses (see Summary of the Invention).

Consistent with appellant's arguments that the claimed vaccination strategy is fatal for the recipient unless the targeted organ is non-essential, it would have been obvious to the ordinary artisan to use PSMA in patients with metastatic prostate tumors and/or patients who have had the prostate tumor removed surgically to elicit antitumor responses in order to treat said cancer patients. Again, Spitler teaches that patients with cancer may have the cancer surgically excised and the be given the subject tumor vaccines (see column 10, lines 39-47) and Andriole et al. teach that surgical excision of the prostate is unsurpassed as a means of controlling organ-confined prostate cancer (see page 13, paragraph 2). Therefore, the prior art is consistent with appellant's arguments that it would have been expected that the prostate would have been removed in prostate cancer patients and the ordinary artisan would not have been concerned with removing a vital organ. Given the removal of the prostate, the ordinary artisan would not have been concerned with the issued raised by appellant that the elicitation of an immune response to an organ-specific antigen results in the eradication of all antigen-expressing cells whether malignant or not.

In response to appellant's assertions concerning the teachings of tumor associated antigens or organ specific antigens in the context of the primary Spitler reference, the rejection set forth above provide a more thorough review of the meaning and understanding of tumor associated antigens (TAAs) by the ordinary artisan at the time the invention was made as well as the asserted tumor uniqueness of the disclosed tumor associated antigens in Spitler.

Appellant's submit that active and passive immunotherapies are distinct and non-overlapping therapies with distinct antigen requirements and cannot be equated. Appellant acknowledges that Israeli and Horoszewicz teach prostate antigens, including PSMA as a target of passive immunity.

Also, it is noted that appellant acknowledges that Horoszewicz teaches active immunization but employs anti-idiotypic antigen rather than antigen, as a fundamentally different therapy. It should be noted that anti-idiotypic antibodies serve as an alternative approach in formulating a vaccine, wherein the anti-idiotypic antibody bears an internal image of the antigen (see page 13, paragraphs 1-2 of the instant specification) (see column 4, lines 24-37 of Spitler). Therefore, anti-idiotypic antibodies serve as alternative to a tumor associated antigen (see page 13, paragraph 2, of the instant specification) (see column 4, lines 24-37 of Spitler; also compare claims 4 and 6 of Spitler). Therefore, tumor associated antigens (TAA) and TAA-specific anti-idiotypic antibodies are alternatives of one another in eliciting active immunization to said TAA.

Note that Spitler is drawn methods and compositions employing liposomes compositions encapsulating or conjugated to tumor associated antigens (TAAs) or anti-idiotypic antibodies to tumor associated antigens (see Summary of the Invention on column 2; also compare claims 4 and 6 of Spitler).).

In contrast to appellant's assertions, appellant's acknowledgment of active immunization with PSMA is consistent with the primary reference Spitler in the use of tumor associated antigens from different sources in active immunization. PSMA was a known tumor associated prostate antigen at the time the invention was made. Appellant has not provided any objective evidence to counter these teachings.

Again, Israeli et al. and Horoszewicz teach PSMA and its expression on prostate tumors (see entire documents)

Given the teachings of Israeli et al. and Horoszewicz that the PSMA / 7E11 specificity is a marker or antigen for prostate cancer; one of ordinary skill in the art at the time the invention was made would have been motivated to substitute the prostate tumor associated antigen PSMA into the methods of stimulating antitumor responses, as known and practiced in the prior art, as taught by Spitler and acknowledged by the specification as to treat prostate cancer.

Given the tissue and tumor specificity of the PSMA / 7E11 specificity as well as immunogenicity as well as its advantages over previous prostate antigens taught by Israeli and Horoszewicz coupled with McCarley et al. teaching that in prostate cancer, monoclonal antibodies prostate antigens are not usually tumor specific (See Abstract and page 298, column 2, paragraph 3 - page 299); one of ordinary skill in the art at the time the invention was made would have been motivated to apply the PSMA prostate antigen in the methods of Spitler to elicit antitumor responses to prostate antigens.

Appellant argues that McCarley, Grauer and Varki have no teaching of suggestion regarding the use of prostate antigens in active immunotherapy.

As indicated above, the application of McCarley, Grauer and Varki have been applied to address appellant's mischaracterization of the phrase "tumor-associated antigen" in the prosecution of the instant application, including its normal meaning and scope in the context of the primary Spitler reference and the applicability of PSMA as a tumor associated antigen.

Appellant argues that Kuby and Cruse are properly prior art to the claimed invention because the instant priority is August 11, 1993.

Again, the general immunology texts and dictionaries of Paul, Kuby and Cruse have been applied to address appellant's mischaracterization of the phrase "tumor associated antigens during the prosecution of the instant application.

Appellant mischaracterizes the Cruse citation by noting the assays of clinical value will probably be developed for class 2 antigens since they are associated with multiple neoplasms and very infrequently found in normal individuals. A more reasonable assumption is that Cruse is referring to diagnostic assays, which need to distinguish between normal and pathologic levels of a particular molecule or tumor associated antigen in this case. Cruse is consistent with the prior art rejection relying upon Spitler's teaching of immunization with tumor associated antigens from prostate and upon the Israeli et al. / Horoszewicz teaching that PSMA is associated with tumors and is a target of tumor immunotherapy at the time the invention was made.

As pointed out previously and above, the majority of tumor antigens are not unique to tumor cells but also are present on normal cells and are called tumor-associated antigens.

There is insufficient objective evidence to support appellant's assertions that Spitler's teaching of active immunotherapy suggests that the use of organ-specific antigens that are also expressed on normal tissues are not candidates for tumor active immunotherapy.

Once a prima facie case of obviousness has been made the burden of going further is shifted to applicant. In re Keller, 642 F.2d 4B, 208 USPQ 871, 882 (CCPA 1981). This appellant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968). See MPEP 2145.

In response to appellant's arguments that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, the teachings of Spitler pertaining to targeting prostate with active immunization of tumor associated antigens and the teachings of Israeli et al. and Horoszewicz that PSMA is such a tumor associated antigen would have led one of ordinary skill in the art at the time the invention was made to combine the references to target prostate tumors by active immunization with PSMA.

The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144

Given the teaching of Spitler for employing tumor associated antigens associated with prostate, it would have been a reasonable understanding by the ordinary artisan at the time the invention was made to employ prostate antigens such as PSMA which was weakly expressed on normal prostate epithelium but strongly expressed on malignant prostatic epithelium. In turn, this differential normal versus malignant expression of PSMA fits within the definition of tumor associated antigens as understood by one of ordinary skill in the art and consistent with the primary reference of Spitler which teaches methods of delivering antitumor vaccines with tumor associated antigens, including prostate antigens (see Summary of the Invention), as well as known methods of delivering said tumor associated antigens to stimulate antitumor responses, encompassed by the claimed invention (see entire document). As pointed out above, appellant has acknowledged that Horoszewicz teaches active immunization with PSMA.

Consistent with appellant's arguments that the claimed vaccination strategy is fatal for the recipient unless the targeted organ is non-essential, it would have been obvious to the ordinary artisan to use PSMA in patients with metastatic prostate tumors and/or patients who have had the prostate tumor removed surgically to elicit antitumor responses in order to treat said cancer patients. Again, Spitler teaches that patients with cancer may have the cancer surgically excised and the be given the subject tumor vaccines (see column 10, lines 39-47) and Andriole et al. teach that surgical excision of the prostate is unsurpassed as a means of controlling organ-confined prostate cancer (see page 13, paragraph 2). Therefore, the prior art is consistent with appellant's arguments that it would have been expected that the prostate would have been removed in prostate cancer patients and the ordinary artisan would not have been concerned with removing a vital organ

Appellant's arguments are not found persuasive.

(12) For the above reasons, it is believed that the rejection should be sustained.

Respectively submitted,

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